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The effects of a clinically feasible application of low-level laser therapy on the rate of orthodontic tooth movement: A triple-blind, split-mouth, randomized controlled trial

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Abstract: INTRODUCTION This split-mouth trial aimed to investigate the effect of low-level laser therapy (LLLT) on the amount of maxillary canine distalization when applied every 4 weeks over 12 weeks. METHODS Twenty-two adolescents and young adults (15 female, 7 male; aged 13-25 years; n = 22) requiring bilateral maxillary first premolar extractions were recruited. After extractions and leveling-alignment, canines were retracted using closed-coil nickel-titanium springs delivering 150 g of force. LLLT was applied to 8 intraoral points on the buccal and palatal sides around the canine root for 10 seconds per point, on day 0, 28, and 56 with the control side receiving sham application. Alginate impressions were taken every 4 weeks on day 0, 28, 56, and 84. The amount of tooth movement, anchorage loss, and canine rotation were measured digitally. Randomization was generated using www.randomisation.com and allocation concealment through sequentially numbered, opaque, sealed envelopes. Participants, operator, and statistic assessor were blinded. Linear regression modeling accounting for clustering within each patient was used to identify differences between LLLT and control sides. RESULTS Twenty-one patients completed the study. The total amount of tooth movement was similar in the LLLT (2.55 ± 0.73 mm) and control group (2.30 ± 0.86 mm), whereas 0.25 mm (95% confidence interval, -0.21, 0.71 mm) of difference was insignificant ($P = 0.27$). No significant differences were found for anchorage loss ($P = 0.22$) or canine rotation ($P = 0.25$). No harms were reported. CONCLUSIONS Application of LLLT every 4 weeks did not result in differences in the amount of tooth movement, anchorage loss, and canine rotation during extraction space closure.

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Title Page

The effects of a clinically feasible application of low-level laser therapy on the rate of orthodontic tooth movement: A triple-blind, split-mouth, randomized controlled trial.

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Abstract

Introduction: The aim of this split-mouth trial was to investigate the effect of low level laser therapy (LLLT) on the amount of maxillary canine distalisation when applied every 4 weeks over a 12-week period. **Methods**: Twenty-two adolescents and young adults (15 females, 7 males; aged 13-25 years; n=22) requiring bilateral maxillary first premolar extractions were recruited. After extractions and levelling-alignment, canines were retracted using closed-coil nickel-titanium springs delivering a 150g force. LLLT was applied to 8 intra-oral points on the buccal and palatal sides around the canine root for 10 seconds per point, on days 0 (T0), 28 (T1), 56 (T2) with the control side receiving sham application. Alginate impressions were taken every 4 weeks on T0, T1, T2 and T3. The amount of tooth movement, anchorage loss and canine rotation were measured digitally. Randomization was generated using www.randomisation.com and allocation concealment through sequentially numbered, opaque, sealed envelopes. Participants, operator and statistic assessor were blinded. Linear regression modelling accounting for clustering within each patient was used to identify differences between LLLT and control sides. **Results**: Twenty-one patients completed the study. The total amount of tooth movement was similar in the LLLT (2.55 ± 0.73mm) and control group (2.30 ± 0.86mm) while the 0.25mm (95%CI -0.21, 0.71mm) of difference was insignificant (p=0.27). No significant differences were found for anchorage loss (p=0.22) or canine rotation (p=0.25). No harms were reported. **Conclusion**: Application of LLLT every 4-weeks did not result in differences in the amount of tooth movement, anchorage loss and canine rotation during extraction space closure.

Registration: The trial was registered in the Australian New Zealand Clinical Trials Registry (Registration number: ACTRN12619001237178).

Protocol: The protocol was not published before trial commencement.

Funding: The study was funded by the Australian Society of Orthodontists Foundation for Research and Education.

INTRODUCTION

There are increasing demands from the patient and clinician perspective to reduce the length of orthodontic treatment time.[1] Methods of accelerating orthodontic tooth movement (OTM) have been investigated not only to satisfy patient and clinician demands, but to decrease the risk of iatrogenic side effects such as root resorption, pain, discomfort, dental caries and to improve compliance.[2-4]

The rate at which a tooth moves following application of orthodontic force is largely limited by the biological processes involved with alveolar bone and periodontal ligament (PDL) remodelling.[5] Externally applied orthodontic force stimulates both pathologic (minor reversible injury) and physiological reactions in the periodontal tissues[6] via creation of areas of pressure and tension within the PDL.[7] This alters the PDL blood flow, stimulating the synthesis and release of key molecules, which recruit and activate osteoclasts and osteoblasts to remodel the PDL, thus resulting in OTM.[5,7] The response of the periodontium to OTM varies with biomechanical signals as well as host factors such as occlusion, metabolism, age and variation in bone form and density.[6] One group of signalling molecules is receptor activator NF-κβ - ligand (RANK-L), a protein found on osteoblast membranes, and its receptor activator NF-κβ (RANK), located on osteoclast precursors. Communication between RANK-L and RANK leads to osteoclast formation and activation.[6] Osteoprotegerin (OPG), is also released by osteoblasts and fibroblasts within the PDL and controls osteoclastogenesis by inhibiting the RANK/RANK-L binding.[6,8]

Procedures to accelerate OTM can involve biological, mechanical and/ or surgical interventions aimed at enhancing these biological processes. A recent survey of orthodontists, patients and parents found that less-invasive techniques were more accepted compared to surgical techniques or the use of intra-oral drugs.[1] Low level laser therapy (LLLT) is a non-invasive and non-surgical technique involving the exposure of cells or tissue to low levels of red and near infrared light (600-1000nm) to alter cellular function and metabolism.[9] Cytochromophores in mitochondria absorb the laser energy, forming adenosine triphosphate (ATP) which, via transcription and protein synthesis, results in increased cellular proliferation and cellular activity of target cells. During OTM, LLLT increases PDL turnover by stimulating osteoclast and osteoblast proliferation and enhancing vascularization and organization of collagen fibers.[9-11] Increased osteoclast and osteoblast proliferation occurs as LLLT augments the RANK/RANK-L and OPG pathways. Using an 808nm, 100mW laser probe on a rat model, Suzuki et al. 2016[12] observed an increase of osteoclastogenesis and RANK-L expression on the compression side and increased bone formation via increased OPG expression on the tension side.

The first human study investigating the effect of LLLT on OTM during canine retraction was by Cruz et al. 2004[13] using a 780nm 20mW GaAlAs diode applied 4 times a month (day 0, 3, 7, 14, 21 of each month) for 2 months. The authors observed a statistically significant increase in the rate of tooth movement in the laser group by 34%. Since this study, several studies have found an increased rate of space closure during OTM using lasers in the 720-810nm range.[14-16] One study found no effect of LLLT on canine retraction although their protocol and parameters differed with higher energy doses of 18.4 joules (J) per session delivered.[17] Currently there is low to moderate evidence that LLLT can increase the rate of orthodontic tooth movement by up to 30%.[18-20] Despite these findings, the optimum wavelength, dosage or power is undetermined.[18,21] Studies using a laser with 810nm wavelength have shown that there is a potential for increased rates of orthodontic tooth movement [14,16,22] however the protocols of laser application (for example multiple days in a month, the first three days of each month or fortnightly application) may not be clinically feasible.

Specific objectives or Hypothesis

The primary aim of this study was to investigate the effect of 4-weekly applications of LLLT on the rate of tooth movement when 150-gram distalization forces are applied to maxillary canines over a 12 week period. Secondary outcomes were to determine if there were any differences in anchorage loss or canine rotation from 4-weekly applications of LLLT.

MATERIAL AND METHODS

Trial design and any changes after trial commencement

This was a triple blind randomised controlled clinical trial. Clinician, participants and person performing the statistical analyses were all blinded to the side allocation. It had a two-arm split mouth design where the right side of each patient was randomised to either an experimental LLLT group or sham control group. A split-mouth design was employed to control any potential patient-related confounders like mouth side, masticatory preference or individual tooth movement potential, as no contamination of LLLT between mouth sides were expected. There were no alterations after commencement of the trial.

Participants, eligibility criteria and settings

Ethics approval was granted by Sydney Local Area Health District, Royal Prince Alfred Hospital Zone (ethics approval numbers X16-0276 and Human Research Ethics Committee/16/RPAH/347).

Twenty-two participants (15 females, 7 males) aged between 13 to 25 years (mean age 17.3 ± 2.5 years) were recruited from the orthodontic waiting list at Sydney Dental Hospital. The selected patients required bilateral extraction of maxillary first premolars and canine retraction with moderate anchorage as part of their orthodontic treatment. Eligible patients were; (1) healthy with no medical conditions or medications affecting the development or structure of teeth, alveolar bone or rate of tooth movement, (2) in the permanent dentition with no craniofacial/dental anomalies or missing teeth, (3) without any previous dental/ orthodontic treatment of the maxillary arch, (4) had no previous orthodontic treatment, (5) had no history of trauma, bruxism or parafunction and (5) no past or present history of periodontal disease.

Verbal and written informed consent were obtained by the patient or guardian (if under 18 years old) and pre-treatment records were obtained prior to commencement of treatment.

Interventions

Maxillary first premolars were extracted uneventfully except one patient who required surgical removal of a premolar root. Patients were then bonded with self-ligating 0.022-inch slot SPEED brackets (Hanson prescription, Strite Industries, Cambridge, Ontario, Canada). A standardised wire sequence of 0.014-in or 0.016-inch nickel titanium (NiTi) (3M Unitek, Monrovia, California, USA) (8 weeks), 0.018 x 0.018-inch 3t Tri-Tanium Memory wire (American Orthodontics, Sheboygan, WI) (8 weeks) and 0.019 x 0.025-inch beta-titanium molybdenum (TMA, 3M Unitek) (8 weeks) was used to achieve levelling and alignment. Anchorage was established using a Nance TPA from the second molars and reinforced with consolidation of the second premolars, first and second molars using a 0.010-inch stainless steel (SS) ligature tie on either side. Canine retraction commenced on an 0.020-inch stainless steel wire using medium super-elastic NiTi closed coil springs (Orthomax, TOMY International Inc., Australia) attached to 5mm powerarms (0.016 x 0.016-inch SS – Dentarum, Ispringen, Germany) from the canine to the first molar (Figure 1). The NiTi coils were set to deliver 150g force, determined using a calibrated spring gauge (Dentarum) and verified at each appointment. Occlusal stops (Transbond Plus Light Cure Band Adhesive; 3M Unitek) were placed on the first molars to prevent any occlusal interference during retraction. Any breakages were rectified within 24 hours else the patient was excluded from the study.

An aluminium gallium arsenide (GaAlAs) laser 808±5nm nm diode, power: 0.20 W, irradiance: 1.97W/cm^2 in continuous wave mode was used (Thor Photomedicine Ltd, Buckinghamshire, UK). LLLT was delivered by applying the laser probe over 8 points per canine tooth (4 buccal, 4 palatal) (Figure 2). The laser output was set at 10 seconds per point, continuous mode. This gave 1.72 Joules (J) of energy per point, a total of 13.87J per visit. LLLT was applied at commencement of canine retraction, day 0 (T0), day 28 (T1), and day 56 (T2) immediately after spring activation. Protective goggles were worn, and patients were irradiated in an enclosed room as per laser specifications. The sham laser function did not deliver any energy output however would perform identically to the test laser function, therefore, and as the wavelength used was not in the visible spectrum, the operator and patient were blinded.

Outcomes (primary and secondary) and any changes after trial commencement

Alginate impressions (Dentalfarm Australia Proprietary, Sydney, Australia) and clinical measurements using digital callipers were taken at T0, T1, T2, and T3 (day 84). Impressions were poured up on the same day and the study models from each time point were scanned by a 3D laser scanner (Trios Model 3, 3D Dental Scanner; 3Shape A/S, Copenhagen, Denmark) onto 3Shape Orthoanalyzer software (version 1.7.1.4; 3Shape A/S) and analysed by one operator (D.M).

Tooth movement was determined by measuring the distance between the distal contact point of the canine to the mesial contact point of the second premolar and comparing these distances over the time points T0-T1, T1-T2, T2-T3 and T0-T3 (Figure 3).

Canine rotation was recorded by measuring the angle between the line created from the mesial and distal contact points of the canine to the mid sagittal plane. Anchorage loss was measured by the distance of the second premolar cusp tip to the most medial point of the third palatal rugae. Both secondary outcomes were taken with reference to the occlusal plane – which was set from the most occlusal tip of the second molars to the most incisal tip of the central incisors (Figure 3).

Sample size calculation

Sample size was set according to previously published split-mouth studies investigating a similar research topic and calculating that a sample of 20 patients is required for obtaining a clinically meaningful difference between LLLT and control side of 1mm with a standard deviation of 0.99mm with alpha=0.05 and a power of 80%.[14,23]

Interim analysis and stopping guidelines

Not Applicable

Randomization (random number generation, allocation concealment, implementation)

Allocation concealment took place through an enclosed internal laser switch where the laser and sham settings were set by a person (A.K.P.) with details unknown to the operator (D.M). The switch casing is enclosed so that the switch settings are concealed from the operator. A description of the switch settings was previously published.[24] The internal switch settings of laser and sham were allocated to a letter A or B and details placed in sequentially numbered opaque sealed envelopes which was revealed after data analysis. At the beginning of the retraction period, the right canine tooth from each patient was randomly allocated to a letter A or B using randomization software (www.randomisation.com) with a 1:1 allocation ratio. The left side of the patient then received the alternate setting.

Blinding

The laser output wavelength (810nm) is not visible to the human eye and does not produce heat; therefore, both the patient and the operator were blinded throughout the study. Laser operator also performed the measurements and was blinded to whether A and B corresponded to laser or sham sides of applications. Statistical analysis was performed with the assessor blinded to whether sides A and B corresponded either to LLLT or control sides and the details were disclosed after supplying the results of the analysis.

Statistical Analysis

Descriptive statistics were calculated including means and Standard Deviations (SD) for continuous variables and absolute/relative frequencies for categorical variables. Since the right/left side of a patient's mouth are correlated, multilevel mixed-effects linear regression modelling of change from baseline values for each outcome with robust standard errors was used to account for clustering and its results were expressed as unstandardized regression coefficients (b) and 95% Confidence Intervals (CI). Correlations for all absolute values for each outcome were calculated to inform future sample size calculations and metaanalyses.[25] All analyses were run in Stata SE 14.0 (StataCorp, College Station, TX) and the dataset was openly provided by the investigators.[26]

All treatment interventions and measurements were taken by a single operator (DM). Repeated measurements of 30 randomly selected digital models were taken 30 days after initial measurements to determine the overall standard error of measurement and the coefficient of variation. To examine measurement reliability and agreement, digital casts at different time points were randomly selected and remeasured after 4 weeks. The concordance correlation coefficient (CCC)[27] and BlandAltman method[28] were used to test intraexaminer reliability and agreement.

RESULTS

Participant flow

Patient flow through the study is illustrated in the CONSORT diagram (Figure 4). Twenty-one patients completed the study which included 7 males (33%), 14 females (66%) with a mean age of 17.4 years (SD: 2.6 years, range 13-23 years). One patient was excluded due to appliance breakage between T2 and T3 where the operator was only notified 4 days after breakage. Patient recruitment began June 2017 and ended April 2018. The LLLT and control groups were similar at T0 in extraction spaces (6.54±1.33mm and 6.09±0.90mm, respectively), canine rotation (38.96±8.81° and 35.44±7.10°, respectively), and anchorage unit position (6.41±3.50 and 6.60±3.01mm, respectively). Calculations indicated within-persons correlations at T3 of 0.55 (contact point measurement), 0.07 (canine rotation) or 0.84 (anchorage loss).

Numbers analysed for primary outcome and subgroup analysis

The means of the amount of tooth movement at each timepoint are shown in Table 1, while the amounts of canine rotation and anchorage loss are given in Tables 2-3. Multiple mixed-effects linear regression analysis indicated no significant difference in treatment effects (change from T0) for contact point measurement (P=0.36), canine rotation (P=0.05), or anchorage loss (P=0.20; Table 4). Furthermore, no significant variation of treatment effects with time was seen, as no statistically significant interaction of treatment with time was found in all cases (P>0.05). Statistically significant increases compared to T1 were seen at T2 and T3 for both space closure (Fig 5) and canine rotation (Fig 6).

Error

The concordance correlation coefficient (CCC) and method error are presented in Table 5 indicating almost perfect agreement in reliability assessment and insignificant differences between repeated measurements.

Harms

There were no reported harms or adverse effects during the laser application or between visits.

DISCUSSION

Main findings in the context of the existing evidence, interpretation

This randomised controlled trial investigated the effects of clinically applicable, 4-weekly applications of LLLT on the amount of orthodontic tooth movement during canine retraction. No clinically or statistically significant differences were noted between the control and LLLT groups in the amount of tooth movement using a GaAlAs laser (808nm, 250mW) with a dosage of 13J per session. Previous studies using a similar wavelength have noted a 30-50% increase in the rate of tooth movement[14-16], however their LLLT applications were very frequent. This included attending for LLLT applications multiple days within the first week of each month, which may not be clinically feasible.

A triple blind split mouth design was employed in the current trial. Great inter-individual variability has been shown in tooth movement studies[29], therefore a split mouth study design limited the effects of inter-individual variability and increased the statistical power.[30] Through the use of an internal LLLT switch, this study was blinded to both the patient and operator, reducing operator bias. Wavelengths in the 780-940nm are not in the visible spectrum and no heat is produced, therefore it is possible to blind the patient. In most previous studies investigating OTM and LLLT, the operator had not been blinded because the control side either involved not turning the laser on[14,16,23]or no laser probe was applied.[15,31] Among the two studies that were double-blinded[17,32], only one of them found a statistically significant difference.[32]

The energy dosage and reduced frequency of application used in this study may have resulted in non-significant findings. Dosages between 2 to 8J per session have been shown to accelerate tooth movement[14,16] whereas a dose of 18.4J per session revealed no difference.[17] It is known that LLLT follows a biphasic dose response curve, where too little energy will fail to elicit a response and conversely too much energy will inhibit biostimulation.[33] Huang et al. 2011 suggests there is a balance between power density and time to produce an optimal result using LLLT, however these parameters are not yet known [33]. The dose used in this study was 13J per session and is intermediary to the doses previously reported. This may imply that either 13J is too high or the LLLT applications every 4-week intervals were not enough to elicit a biostimulatory effect.

An increase in proliferation of human PDL fibroblasts is noted in vitro using a GaAlAs diode (809nm, 10mW with either 2, 4 or 8J/cm^2) for up to 72 hours after irradiation, with the effect decreasing after 48 hours.[34] In an animal study investigating the rate of bone formation during rapid maxillary expansion in rats, it found that daily and early irradiation had a 35% increase in newly formed bone whereas a one-time irradiation, delivering the same total energy dose, had no effect. A recent study using LLLT applications every 3 weeks, showed roughly a 2-fold increase in the amount of tooth movement when using a 940nm, 100mW GaAlAs laser with a dose of 7.5J/cm^2.[23] The differences in findings may be due to different LLLT dosage or in the time intervals between applications. However, in that study the operator was not blinded, there was a shorter investigation period of 2 months and extractions were performed within a month before canine retraction, which may have induced the regional acceleratory phenomenon (RAP) effect and skewed results. The two aforementioned double-blind studies applied LLLT on the first 3 days of each month and found differing results, which may be explained by the differences, in wavelengths and dosages.[17,32]

The ideal wavelength for stimulating OTM with LLLT is not yet known and there may be no direct relationship with LLLT efficiency.[11,35] An animal study investigated the effects of two different 630nm and 850nm GaAlAs, with a dose of 27J and 8J respectively, and observed a reduction in OTM in both laser groups compared to the control.[36] Conversely, in human studies, there is low to moderate quality evidence that wavelengths between 780nm to 940nm have been shown to accelerate OTM[13,14,16,22,23,31,32] with one study using 860nm that showed no difference[17]. The depth of penetration of laser irradiation is dependent on wavelength as well as the absorption and scattering characteristics of the target tissue[37]. Wavelengths of 830nm, similar to the wavelengths used in this study, have a penetration of 30-40mm [37] while there is a 6.81% loss of laser energy per millimetre of alveolar bone, with minimal effect of gingival thickness. This may have resulted in less energy delivered to the canine PDL and subsequent inability to stimulate increased OTM, especially on the palatal side due to the greater thickness of palatal bone.

With varying outcomes in LLLT research, caution should be advised before clinical implementation of LLLT to accelerate OTM. As discussed, the optimal wavelength and dosage are yet to be determined. The specifications to apply LLLT in our study required the patient and operator to wear protective eyewear and be in an enclosed room. Although patient acceptance may be higher compared to more invasive techniques[1], the practicality of delivering LLLT in an orthodontic practice should be considered. Whilst patient co-operation is eliminated, the price of equipment, increased chair time, potential need for an isolated room, and LLLT training would need to be considered and weighed against the potential reduction in treatment duration.[18] In the future, portable devices may be an alternative solution if they become more affordable.

There were slightly higher amounts of canine rotation in the LLLT group which was non-significant with both groups displaying a wide variability of rotation. The use of self-ligating SPEED brackets in this study helped to standardise the effect of ligation on both sides as well as reduce the frictional effects placed on the canines during retraction. The small bracket width and retraction on a round stainless steel wire may have reduced some control of canine rotation during retraction; however, self-ligating brackets and round stainless steel wires were used for canine retraction in order to maintain force levels and reduce the effects of force loss due to friction.[38]

Minimal anchorage loss was noted, with 0.66mm on the LLLT side and 0.36mm on the control side. Although skeletal anchorage may have been used to maximise posterior anchorage, it was decided against to minimise failures and reduce patient morbidity during the trial and would have contradicted the minimal invasive nature of the trial. Anchorage loss was not considered in some of the previous studies[14] and is an important factor in determining if the LLLT may affect surrounding teeth such as the second premolar.

Limitations

The depth of laser penetration is determined by the patients' anatomic tissue characteristics such as bone and gingival thickness;[37] however, this affects only the specific area of interest around the tooth were the laser is pointed and does not results into any contamination across groups. A distalisation force of 150g was applied to the canine tooth and was monitored at each time-point; however, gingival impingement of the coil or a small drop in force levels (less than 20g) was noted at some of these time-points and the coil was readjusted to 150g force. This change in force magnitude may have altered the amount of OTM; however, this is something that can happen in the everyday clinical practice. In addition, space closure has been measured as changes in the distance between the canines and the second premolars. The movement of the canine centre of mass with a superimposition of the sequential casts could not be performed because the presence of the Nance-TPA anchorage device covered the palatal rugae in some patients and this did not allow consistent visualisation and availability for superimposition on these stable anatomic areas. Currently there are no definitive clinical guidelines for the optimum dosage or frequency for LLLT to increase the rate of tooth movement.[18,39] Further research is required to determine the optimal protocol[40] or if there is a relationship between different laser parameters and the effectiveness of LLLT.[19] Varying degrees of bias in current studies weaken the level of evidence to make firm conclusions regarding the effect of LLLT on orthodontic tooth movement.[21] Energy dosage and application frequency may be more important than wavelength and this should be investigated in further studies.

Generalizability

LLLT is a safe, non-invasive and compliance-free modality; however, the specific LLLT parameters used and the monthly applications in adolescents and young adults, did not elicit any notable differences on the amount of tooth movement. The GaAlAs laser diode set at 808nm, 250mW, 1.97W/cm^2 irradiance) with an applied dose of 13J per session every four weeks could not stimulate increased tooth movement. There are many variables determining LLLT dosage and energy delivery through tissues. This study highlights the importance of further research into LLLT dosimetry and application schemes for drawing clinical recommendations.

CONCLUSIONS

No significant differences were noted in the rate of orthodontic tooth movement with applying LLLT every 4 weeks at 13J per session. Although LLLT has been previously shown to enhance the rate and subsequent the amount of tooth movement in some studies that used more frequent applications, the clinically practical monthly LLLT applications used in this study were not able to elicit any increases in tooth movement during maxillary canine distalization for extraction space closure.

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HIGHLIGHTS

- The effect of low-level laser therapy (LLLT) on canine distalization was assessed on maxillary premolar extraction space closure.
- The amount of tooth movement was similar in the LLLT and control sides.
- No differences were found in anchorage loss and canine rotation between the two sides.
- LLLT did not influence the amount of orthodontic tooth movement when applied every 4 weeks.

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<u>Figure Legends.</u>

Figure 1. Canine retraction set up A) buccal view, B) occlusal view at T0.

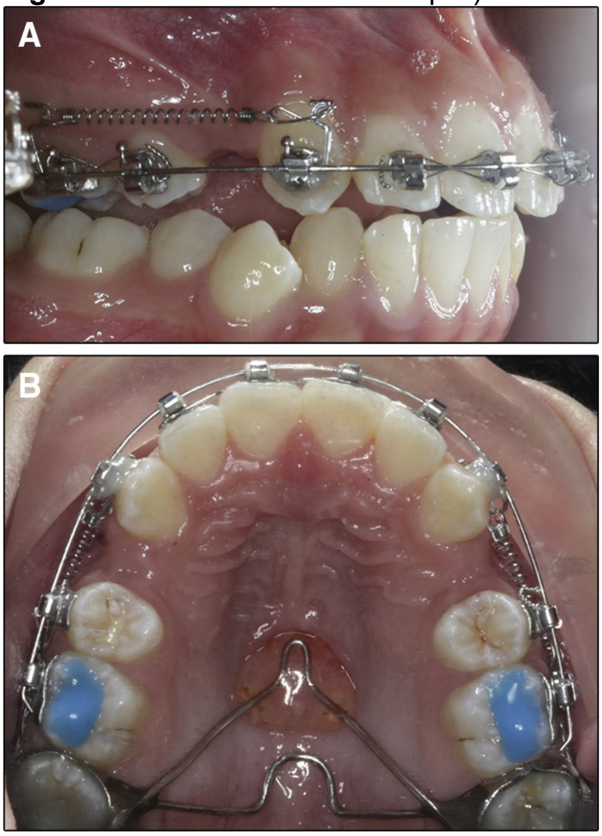


Figure 2. Laser application points on the canine from the A) buccal view and B) palatal view. 4 application points were used on the buccal and palatal. These points were mesiobuccal to the gingival area of the root, distobuccal to the gingival area of the root, the mid apical root and the apical third of the root.

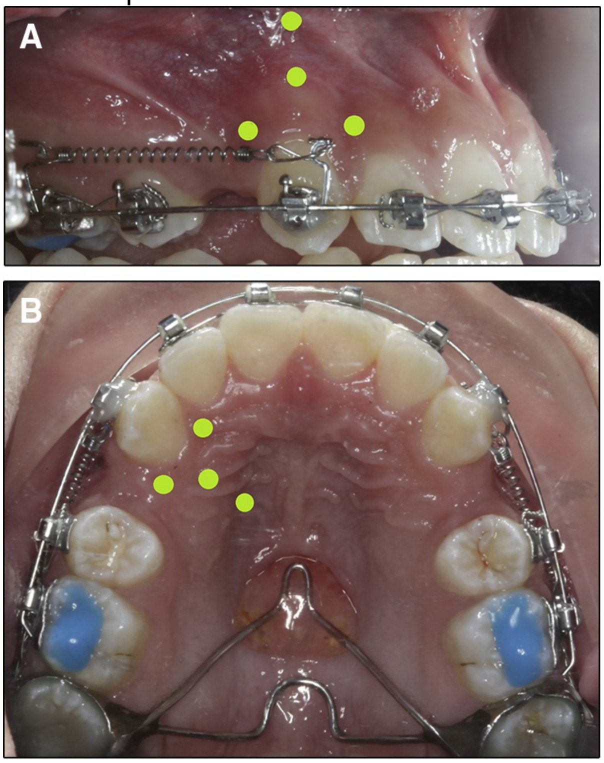


Figure 3. Digital measurements. **A)** Tooth movement was measured from the most distal contact point of the canine to the most mesial contact point of the upper second molar in a 3D view. **B)** Anchorage loss was measured on the occlusal view of the digital models as the distance from the distal contact point of the upper second premolar to the most mesial point of the third palatal rugae via projections to the mid sagittal plane (MSP). Canine rotation was measured as the angle from the line through the mesial and distal contact points of the canine to the MSP.

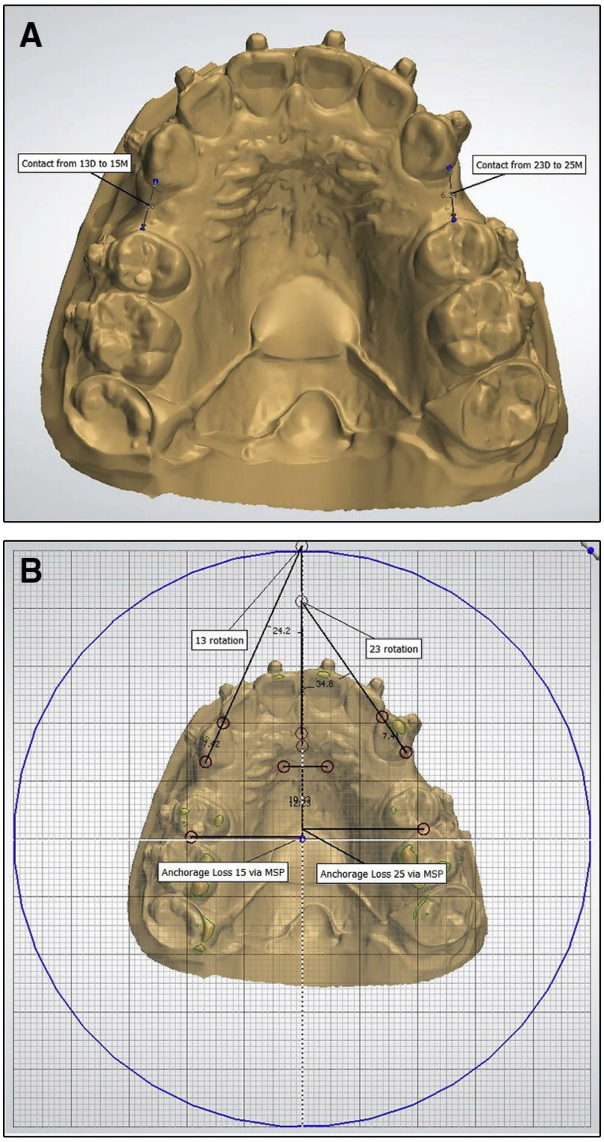


Figure 4: Consort Patient Flow Diagram

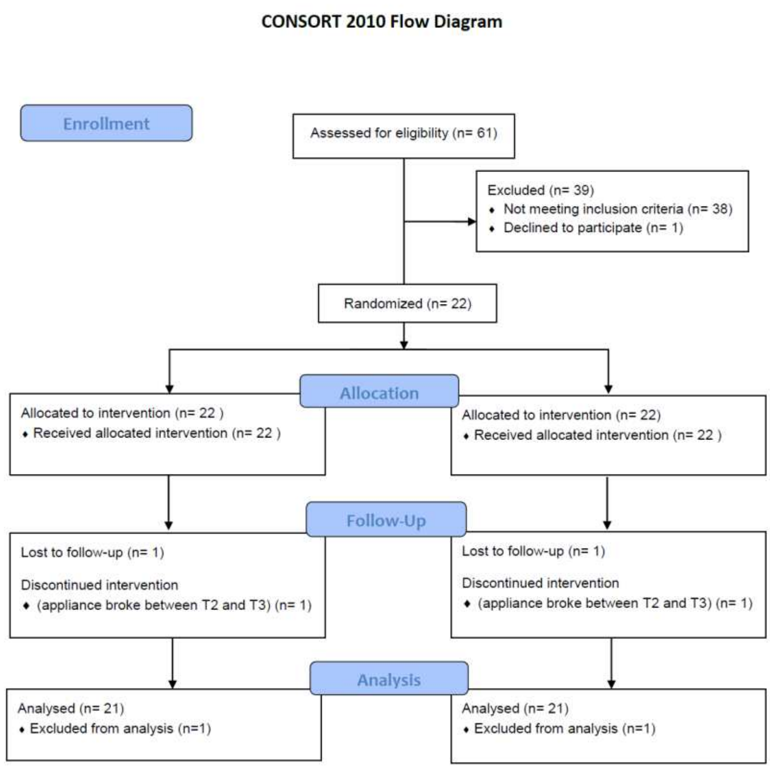


Figure 5: Line chart indicating contact point measurement (space closure) at 0 weeks (T0), 4 weeks (T1), 8 weeks (T2) or 12 weeks (T3).

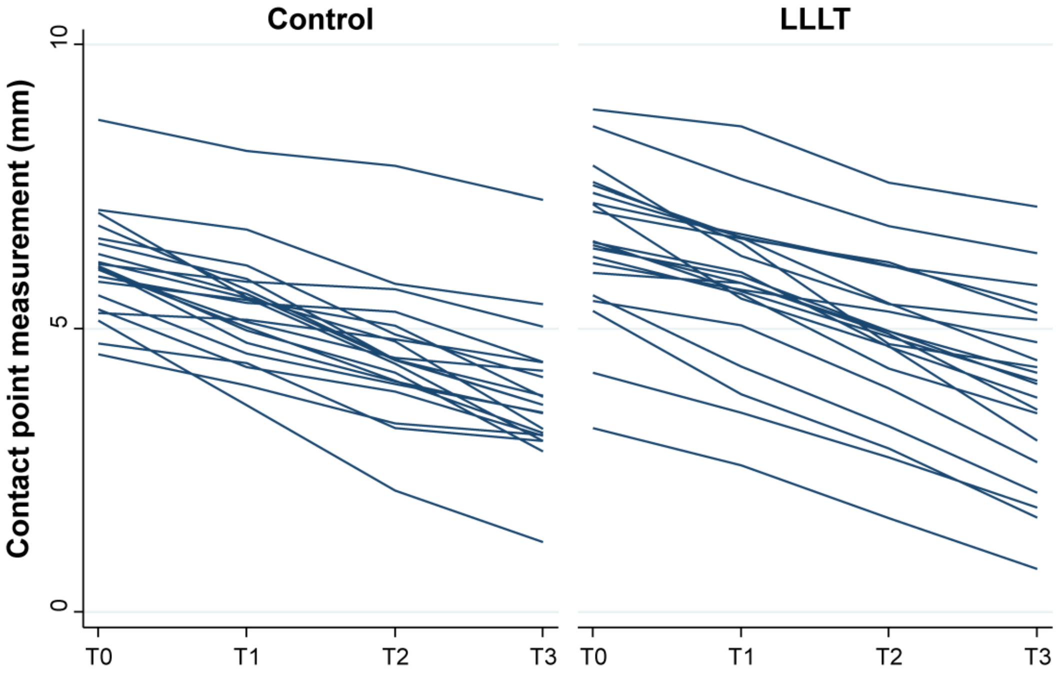
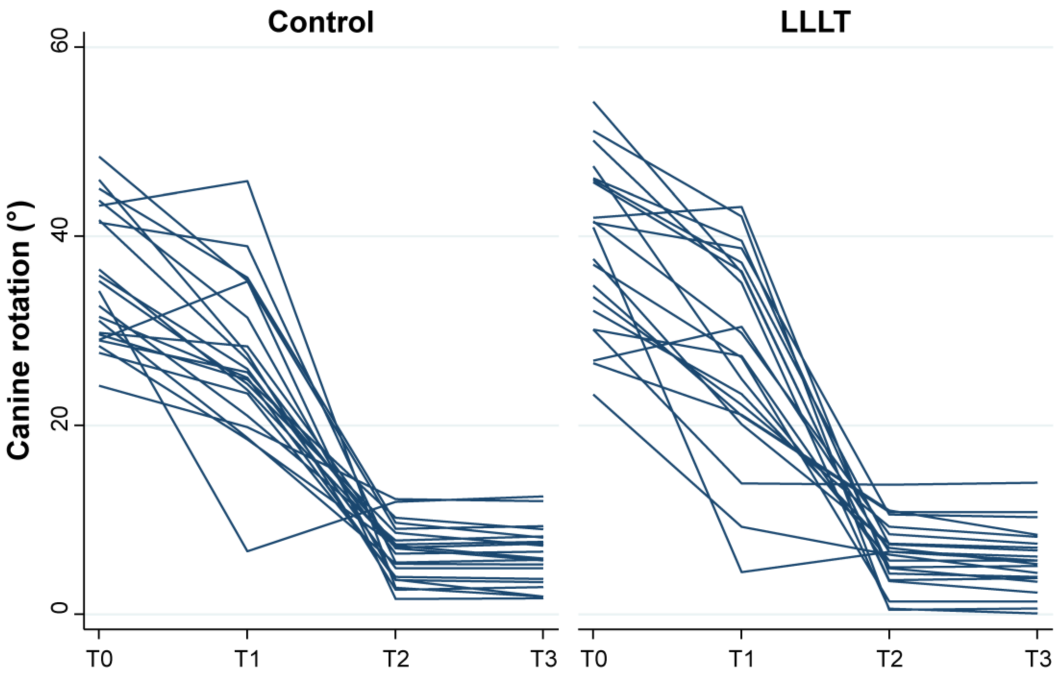


Figure 6: Line chart indicating canine rotation at 0 weeks (T0), 4 weeks (T1), 8 weeks (T2) or 12 weeks (T3).



TABLES

Table 1. Amount of tooth movement in the Low Level Laser Therapy (LLLT) and Control sides with comparisons between them given as mean±SD.

	ABSOLUTE VALUES			CHANGE FROM T0	
Time	**LLLT**	**Control**		**LLLT**	**Control**
T0	6.54±1.33	6.09±0.90		-	-
T1	5.75±1.35	5.33±0.98		0.79±0.41	0.76±0.41
T2	4.83±1.40	4.54±1.12		1.71±0.56	1.55±0.66
T3	3.99±1.61	3.79±1.18		2.55±0.73	2.30±0.86

LLLT, low level laser therapy; SD, standard deviation.

Table 2. Amount of canine rotation in the Low Level Laser Therapy (LLLT) and Control sides with comparisons between them given as mean±SD.

	ABSOLUTE VALUES			CHANGE FROM T0	
Time	**LLLT**	**Control**		**LLLT**	**Control**
T0	38.96±8.81	35.44±7.10		-	-
T1	27.75±10.68	26.78±8.39		11.21±8.65	8.66±7.39
T2	6.41±3.50	6.60±3.01		32.55±11.12	28.84±9.05
T3	5.75±3.43	6.24±3.08		33.21±10.71	29.20±9.00

LLLT, low level laser therapy; SD, standard deviation.

Table 3. Amount of anchorage lossn in the Low Level Laser Therapy (LLLT) and Control sides with comparisons between them given as mean±SD.

	ABSOLUTE VALUES			CHANGE FROM T0	
Time	**LLLT**	**Control**		**LLLT**	**Control**
T0	6.41±3.50	6.60±3.01		-	-
T3	5.75±3.43	6.24±3.08		0.66±0.78	0.36±0.78

LLLT, low level laser therapy; SD, standard deviation.

Table 4. Results of the multilevel mixed-effects linear regression on change for each outcome from T0 accounting for within-patient clustering with robust standard errors. Interaction terms of treatment group-with-time were introduced for each outcome, but were dropped as they were non-significant.

		Contact point measurement			**Canine rotation**			**Anchorage loss**	
Factor	**Group**	**b (95% CI)**	**P**		**b (95% CI)**	**P**		**b (95% CI)**	**P**
Treatment	Control	Reference			Reference			0.30 (-0.16, 0.76)	0.20
	LLLT	0.15 (-0.17, 0.47)	0.36		3.42 (0.03, 6.81)	0.05			
Time	T1	Reference			Reference			-	
	T2	0.85 (0.75, 0.96)	<0.001		20.76 (16.44, 25.08)	<0.001		-	
	T3	1.65 (1.46, 1.84)	<0.001		21.27 (16.98, 25.56)	<0.001		-	

b, unstandardized regression coefficient; CI, confidence interval; LLLT, low level laser therapy.

Table 5. Method error assessment of repeated measurements.

Outcome	CCC (95% CI)	Average difference	95% limits of agreement	P*
Contact point measurement	0.993 (0.988, 0.996)	0.039	-0.290, 0.368	0.21
Canine rotation	0.982 (0.945, 0.994)	-0.046	-3.782, 3.689	0.58
Anchorage loss	0.994 (0.982, 0.998)	0.043	-0.479, 0.565	0.84

CCC, concordance correlation coefficient; CI, confidence interval. * from Bradley-Blackwood test